

Schedule I Control Status Does Not Impede Legitimate Nonclinical Research in the United States

Gauvin DV* and Zimmermann ZJ

Neurobehavioral Sciences Department, Charles River Laboratories, Inc, 54943 North Main St., Mattawan, MI 49071, United States

Abstract

Background: There are many misconceptions about conducting research with Schedule 1 (CI) controlled substances to conduct nonclinical research in the US. Research design cannot be driven by financial constraints.

Aim: The notion that current regulatory control of CI drugs hamper, hinders, or restricts legitimate nonclinical research in the U.S. may reflect a lack of understanding of the procedures in place to study these drugs.

Review: Nonclinical research must comply with the Good Laboratory Practice (GLP) guidelines (21 CFR §58) of the U.S. Food & Drug Administration (FDA). Protocol development under the GLPs provides the information and details required under the Controlled Substances Act (CSA) for submission to the two drug regulating agencies relevant to the approvals required prior to the first dose administration on the study. Under 21 USC § 823(f), the registration applications by practitioners wishing to conduct Schedule I research shall be referred by the Secretary of HHS (FDA), who shall determine the qualifications and competency of each practitioner, as well as the merits of the research protocol. Additionally, a formal verification of the professional standards of the Study Director and the research facility conducting the study will be conducted by the DEA. These additional two requirements differentiate studies conducted with CI drugs and all other schedule-controlled drugs. In the U.S., the security requirements for storage under current DEA administrative regulations are equivalent for both CI and CII drugs. **Conclusion:** An informed researcher conducting nonclinical studies with CII– CV drugs can easily comply with current drug control requirements to conduct research with CI drugs in the US.

Keywords: Nonclinical research; Controlled substances; Schedule I drugs

Introduction

Out of concern for the public health and well-being, the international community of scientists and health care advocates recognized that drug addiction constitutes a serious public health concern and is fraught with social and economic impact to societies. In considering effective measures against drug abuse, an integrated and common action plan was initiated that called for international cooperation guided by common legal principles aimed at common objectives codified in the Single Convention on Narcotic Drugs [1]. Under the 1961 international treaty obligations, access to addictive substances was not accepted to be an inalienable or inferred “human right.” Addictive drugs were controlled under a common regulatory system created to prioritize the legitimate use of, and access to therapeutic drugs for medical and research purposes. The target of control is, in general, drug substances. Drug substances are placed in one of five respective schedules based on whether they have a currently accepted medical use in treatment in the United States, their relative abuse potential to other known drugs-of-abuse, and likelihood that use of the substance outside the scope of medical practice will produce dependence. Compliance with the treaties is vital for the realization of the right to health. International drug control treaties require State Parties to ensure the access, availability and rational use of internationally controlled narcotic drugs and psychotropic substances for medical purposes. The United Nations has promoted national and international measures for adequate availability of internationally controlled drugs for medical purposes so that access is not unduly restricted. The treaties were codified into law by the US Congress in 1970 in the Comprehensive Drug Abuse Prevention and Control Act (Public Law 91–513, 84 Stat. 1236); now, commonly referred to as the Controlled Substances Act (CSA). The CSA was implemented to establish the Drug Enforcement Administration (DEA) with the aim and provisions for full and open access to all drug substances determined to be “medicines” approved for use under medical supervision and for bona fide scientific research. In the early years of

the “medical marijuana movement” pro-drug advocates began a public campaign against established drug control policies to have unfettered access to marijuana, which was placed into Schedule 1 (CI), the most restrictive schedule of the five. Following the passage of the CSA there were directed attacks of the legal and legitimate professional avenues to drug supplies for “studies” of public interest that may have lacked any scientific merit or rigor (example, marijuana). The rejection of poorly designed protocols that had limited scientific justification or that proposed to use methodologies that did not meet the standards set by the National Institutes of Health (NIH), industry best practices, and the drug control policies themselves were presented by the public press as a “ban on legitimate drug research”. In a published final rule by the DEA in 1992, some of these early research projects were identified as follows: During the 1970’s and 1980’s, a number of states set up research programs to give marijuana to cancer and glaucoma patients, on the chance it might help. Some people point to these programs as proof of marijuana’s usefulness. Unfortunately, all research is not necessarily good scientific research. These state programs failed to follow responsible scientific methods. Patients took marijuana together with their regular medicines, so it is impossible to say whether marijuana helped them. Observations or results were not scientifically measured. Procedures were so poor that much critical research data were lost or never recorded. Although these programs were well intentioned, they are not scientific proof of anything. In retrospect, some of these early

*Corresponding author: Gauvin DV, Neurobehavioral Sciences Department, Charles River Laboratories, Inc, 54943 North Main St., Mattawan, MI 49071, United States, E-mail: david.gauvin@crl.com

Received March 30, 2019; Accepted April 29, 2019; Published May 12, 2019

Citation: Gauvin DV, Zimmermann ZJ (2019) Schedule I Control Status Does Not Impede Legitimate Nonclinical Research in the United States. Pharmaceut Reg Affairs 8:1.

Copyright: © 2019 Gauvin DV, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

study requests may have represented cases of poor science. The drugs of interest were always drugs that were internationally controlled based on the lack of valid and reliable data demonstrating “acceptable medical use” (therapeutic efficacy) and “safety under medical supervision” (for example, marijuana, ecstasy, and psilocybin), that is, Schedule I drugs (CI) [2]. These conclusions were further supported by Cohen and in the formal rejection letter to a Principal Investigator of a marijuana study by the Director of the NIDA [3-5]. Under the CSA, the term “practitioner” includes scientists (Ph.D.), physicians, dentists, veterinarians, hospitals, pharmacists, or other DEA registrants who conduct bona fide research in universities, contract research organizations, private and public research foundations, hospitals and analytical laboratories (21 USC §802 [21]). These practitioners are registered with the DEA in order to formulate and dispense controlled substances (CSs) as part of nonclinical (animal) or clinical (human) research protocols initially approved by their own Institutional Animal Care and Use Committee (IACUC) or the Institutional Review Boards (IRB). The FDA’s scientific assessment determines the safety and efficacy of drugs intended for human consumption. The FDA’s team, charged with conducting that assessment, consists of clinical pharmacologists, epidemiologists, toxicologists. Physicians, chemists, statisticians and other scientists, working together to ensure approved drugs are safe and effective. As recently quoted by the DEA Administrator, the Department of Health and Human Services has defined an expert (in this discipline) as “an individual qualified by scientific training and experience to evaluate the safety and effectiveness of a drug. Although medical doctors are highly trained and qualified to treat patients with FDA-approved drugs, “medical practitioners who are not experts in evaluating drugs are not qualified to determine whether a drug is generally recognized as safe or effective or meets NDA (New Drug Application) requirements.” (57 CFR 10499). Simply put, evaluating the safety and effectiveness of drugs for their intended use is a highly specialized endeavor undertaken by the FDA’s Center for Drug Evaluation and Research [6]. All protocols that include the use of CI substances must also be submitted for regulatory review prior to purchasing the CI substances and the initiation of the study. This requirement is not limited to just IND-enabling studies. For nonclinical research studies such as discovery, efficacy, pre-IND, IND, and NDA-enabling animal research protocols must be reviewed by FDA and DEA prior to purchasing any CI substance. Clinical protocols must be submitted directly to the FDA and nonclinical protocols are submitted to the DEA for forwarding onto the FDA. To ease the review process for a newcomer to CI research, details of what must be submitted to the agencies for review are discussed, below. The process of regulatory agency review of study protocols is certainly not new for pharmaceutical companies or Contract Research Organizations (CROs) who are actively engaged in product development of new molecular entities. For the novice in the process of CI clinical or nonclinical abuse liability research, the FDA has resources available and pathways for seeking advice [7]. To provide a balance of regulatory control that ensures the health and safety of the public and the research goals of the practitioner, there is an established and simple review process in place for planning formal meetings between the FDA and Sponsors or Applicants of all new therapeutic drug products. The researcher conducting studies with CI drug substances can utilize this agency service “free of charge” to help them in the protocol development stages of their research. The “CDER 21st Century Review Process Desk Reference Guide (DRG)” describes the review activities required for all new drug and biological license applications, including procedures designed to meet the principles and timelines described in FDA’s “Guidance for Review Staff and Industry: Good Review Management Principles and Practices for

PDUFA Products”, and process requirements described in the PDUFA V agreement entitled “PDUFA Reauthorization Performance Goals And Procedures For Fiscal Years 2013 Through 2017” [8-10]. The DRG is intended for use in the review of New Drug Applications (NDAs), Biologics License Applications (BLAs) and efficacy supplements, but it can be helpful in the general research arena that is conducting research using CI drugs. The younger scientist interested in conducting clinical research with CI drugs should take advantage of the Center for Drug Evaluation and Research’s (CDER) existing collaborative program designed to foster early communications between the scientist and the new drug review divisions [11]. In addition to explaining the steps in the review process, the DRG outlines expectations for the FDA reviewer to conduct and provide timelines for completion of the various review milestones. The DRG describes the roles of review participants and signatory authorities and includes suggestions for working in a team environment to complete a timely, high-quality review. The objectives of the DRG are to provide a resource for the researcher or drug development teams and to direct them to the appropriate CDER staff members who can help define characteristics of a successful review process, such as CI protocol reviews. In the case of CI drug substance related research, this process would involve the Controlled Substance Staff (CSS) in the CDER at FDA. This is part of the researcher’s responsibility in conducting “due diligence” in proposing to conduct research with drugs that have been internationally controlled because they have been deemed to have no accepted medical use. In this context, the “legal” or regulatory term “due diligence” is defined as the care that a reasonable person exercises to avoid harm to other persons or to exercise the necessary background information and process required to conduct Schedule I research within the constraints of existing laws and regulation governing controlled substances. Due diligence with regards to the actual conduct of scientific research with CI drugs refers to the inquiry and understanding of the potential investment of time and effort required to conform to industry best practices when conducting valid, reliable and sound scientific methods to safely conduct research with humans or purpose-bred laboratory animals. Research design cannot be driven by financial constraints. The focus of this report is on research conducted with CI substances in nonclinical safety and toxicology studies, only. It is not our intent to address clinical research programs. Nonclinical research intended for Investigational New Drug (IND) submissions or NDAs must comply with the Good Laboratory Practice (GLP) guidelines (21 USC §58) of the FDA. Protocol development under the GLPs provides much of the information and details required under the CSA for submission to the two drug regulating agencies relevant to the approvals required to conduct research with CI substances prior to the first dose administration on the study. When compiled by the pharmaceutical drug developer or its affiliates, the full research review package should include all of the discussion points described below and be submitted to one of the 222 DEA Domestic Offices located in one of 23 DEA Divisions within the continental U.S. For example, Michigan registrants would submit the information to the Detroit Divisional Office of the DEA, Illinois registrants would submit to the Chicago Divisional Office, etc. All items listed below must be included in the review package sent to the DEA and FDA. The DEA Divisional Office staff will conduct the initial review of the research package to ensure that the research facility, or scientist (Study Director) is 1) licensed to conduct bona fide research with CI controlled substances, 2) to verify that the license itself includes approval for the specific DEA drug codes listed in the protocol, and 3) review that the current security programs in place at the research facility are adequate for the specific drug substance and quantities of substances being requested (see “Security Requirements section,

below) [12]. The Division Office staff will then forward the submitted research package to DEA Headquarters. Under 21 USC § 823(f), the full CI drug control review is ultimately conducted by staff members of the Drug and Chemical Evaluation Section of the Office of Diversion Control at DEA Headquarters in Arlington, VA. Subsequently, the protocols are referred to the Secretary of HHS (FDA) by email, FAX, or interagency communications. The FDA will determine the qualifications and competency of each practitioner, as well as the scientific merits of the research protocols by members of the CSS in CDER. All drugs listed in Schedule I have no currently accepted medical use in treatment in the U.S. and therefore may not be prescribed, administered, or dispensed for medical use. The CSA allows for bona fide research with substances in CI, provided that the FDA has determined 1) that the researcher is qualified to conduct the research and 2) based on his/her background, education and experience the researcher is competent, and provided further that the FDA has 3) determined the research protocol to be "meritorious." (for defining characteristics see sections below) [13]. Researchers who meet these criteria must obtain a separate registration to conduct research with a Schedule I CSs. In contrast, drugs listed in Schedules II through V all have some accepted medical use and therefore may be prescribed, administered, or dispensed for medical use by licensed health care professionals (doctors, dentists, veterinarians, etc.). A registrant requesting to conduct research with CI substances must acknowledge that they are proposing dose administrations of a drug substance that has not been accepted to be safe even under medical supervision. This may minimally impact nonclinical research protocols that is being conducted to provide data for an IND application or NDA. It is highly recommended to conduct and develop these animal-based study protocols in full compliance with GLP guidelines to ensure adequate information is provided to FDA for this review. In establishing GLP compliance, the nonclinical protocols submitted to the Sponsor by research institutions, academic laboratories, or contract research organization for review and approval can be the identical protocols submitted to DEA and FDA for regulatory review. Despite what it may seem the DEA Administrator recently reported that of the nearly 600 protocols submitted for review as of January 2018, every protocol had been approved [14]. In actuality, gaining approval for legitimate and well-designed nonclinical studies that include the use of CI substances is no more difficult than submitting the protocol for a Public Health Services Grant application (PHS) to the National Institutes of Health. Based on Charles Rivers' experience as a nonclinical Contract Research Organization (CRO), the process of regulatory review and approval for use of CI drug substances provides no more restrictions, hindrances, or difficulties than any other standard GLP compliant sponsor-requested study preparation. The claims of government interference or hindrance in this process are more likely related to a lack of first-hand experience in this relatively small research arena [15-23].

Drug Security Concerns

By the very nature of nonclinical research conducted with all CSs there is an implied understanding and fiduciary responsibility of the researcher/practitioner to prevent loss, theft, and diversion of the drugs under their immediate care during the conduct of the research. It is not just drug control security that federal regulators are concerned about. It is understood that many individuals within a testing facility will have direct access to study data. They may also have access to bulk product, formulations containing the product during the normal day-to-day operations of the GLP-compliant protocol requirements. Existing drug storage, handling, and administration procedures may have been given a prior approval by DEA agents during the license review process prior

to any request for CI drug bulk material purchase is even made. Wiley et al. have presented a case study of the hijacking of findings from basic research facilities conducting approved studies with CI controlled substances (cannabinoids) [24]. During the process of animal research, "look-alike" products were found in black market supplies as a result of the intentional diversion of information and material samples from the laboratory. However, the actual loss or diversion of drug substance from the laboratory is not necessarily the direct cause of street-side supplies of novel CI drug substances. Nichols published research findings on p-methylthioamphetamine (MTA, aka "flatliners") in professional journals in the early 1990s [25]. These published reports were the source for a "laboratory-adept European entrepreneur" and his chief chemist, to manufacture and sell the hallucinogenic amphetamine without the full preclinical assessment of the drug's safety [26]. Other researchers have voiced similar concerns against drug control policies, in general [16,27]. All avenues of access to the drug and related information can lead to diversion to the general public. These are the constant concern for the World Health Organization (WHO) and US DEA and should also be the concern of every researcher conducting bona fide preclinical drug development research. In order to minimize the opportunities for theft or diversion of controlled substances, researchers have an obligation not only to provide effective physical security, but also to initiate additional procedures to reduce access by unauthorized persons as well as to provide alarm systems, where necessary. This would seem intuitive to the average practitioner who focusses their research efforts on CSs, in the first place. There is a handbook that details the appropriate security requirements to conduct research with CSs available on the DEA website [28]. An overall evaluation of the researcher's security will be made by DEA prior to issuing the initial CI license using the general and minimal security requirements outlined in the security manual to assure that the CSs are stored securely. Of special note here is that the security manual sets equivalent minimum standards for both CI & II controlled substances. DEA evaluates a registrant security system on both an element-by-element and an overall basis, measuring the current security system against the potential theft or diversion problem the registrant might encounter at the registered location with CI substances. However, the *minimum standards* and general security requirements set forth for CI controlled substances are the same as for CII drug substances. If a physician or researcher has a DEA approved CII license, there may be no added costs or efforts in bringing in CI substances into the testing facility for research purposes. Some of the factors considered when evaluating a test facility's security include:

1. The number of employees who have access to the controlled substances.
2. The location of the registrant (high or low crime area).
3. Use of an effective alarm system.
4. Quantity of controlled substances to be kept on hand.
5. Prior history of theft or drug diversion within and around the general locale of the research facility.

The security systems may be different if the research is being conducted at a University laboratory (for example, at an urban school like Wayne State University) which is located in the center of a large metropolitan city (Detroit, MI) with a history of urban blight and high crime rates, compared to Charles River Laboratories, Inc.), located on the opposite side of the state, in a small town (Mattawan) within a farming community near a state-funded university (Western Michigan University) [29,30]. It seems intuitive that the security requirements to handle bulk CI materials may differ if the protocol requires grams of

bulk product or 10's of kilograms of product. An overall evaluation of the practitioner's security will be made by DEA investigators visiting the site and using the general and minimal security requirements, as outlined in the security manual, to ensure that the CSs will be stored securely.

Protocol Development and Documentation for DEA Review

The DEA protocol review is free of charge and the "turn around" time for this process under current policies is approximately 60 to 90 days. The Drug and Chemical Evaluation Section of the Office of Diversion control is assigned this agency purview. The DEA needs sufficient information contained within the submitted protocol that will allow the drug control agency a full and adequate picture of who, what, and where the research will be conducted. The DEA is not so much concerned with the "why" of the research protocol – that will be the job of the FDA review. The materials submitted for review are detailed within the CSA:

- A. The local division office of the DEA will verify past and present regulatory inspections of the facility proposed to conduct the research. The local division office's diversion investigators will determine if there are any changes in current structural or procedural security plans needed for the specific drug and/or drug quantities needed and listed in the protocols. Research facilities in today's nonclinical testing environments are usually maintained at high standards in response to regularly scheduled inspections by FDA, EPA, the USDA, and AAALAC. This should not be associated with a large monetary or time/effort investment in the contemporary research environment.
- B. The researcher's federal license must be active and unrestricted. The Office of Drug Registration (ODR) is responsible for verification of the registrants' license and current legal status with the individual State's Board of Pharmacy of which the registrant must hold a tandem state license to conduct CI research.
- C. The full curriculum vitae of the organization's personnel (21 CFR §58.29) involved and listed in the study protocol must be supplied for review. This would include the Study Director, Alternate Contact, the CI registrant holder, all Contributing Scientists for Control Article formulations and analysis, etc.
- D. DEA registrations are site location (street address) specific. If there is more than one building involved in the research project with different physical addresses, then both CI licenses must be listed and provided to the agency for review. For example, a hospital pharmacy used for storing or formulating the drug dose vials for use in dosing animals that may be housed in vivariums or test rooms in an ancillary research building on campus (with another street address) may require two licenses.
- E. Background checks with local, state, and federal crime databases must be conducted to ensure that the researcher is in good standing with relevant medical associations and have no outstanding felony warrants, cases, investigations or felony convictions unknown to the DEA, at the time. Such legal entanglements may jeopardize the applicant's ability to hold the state and federal licenses and complete the proposed study.
- F. The total amount of CI bulk material for the full study must be estimated to the best ability of the SD based on the total number of animals proposed and the expected bodyweight changes

over the study duration based on historical control growth charts for the species, strain, and gender of animals being used. The bulk estimate of need must also account for the realistic expectations of intentional loss of material during the conduct of the study such as formulation sample collection and analysis as well as any expected operationally-driven formulation losses (e.g., syringe hub loss, etc.).

- a) The prior inspection of the facility by DEA for the initial CI registration approval would have reviewed and accepted the facility's standard operating procedures for loss, spillage, and disposal of residual test material that is not used, contaminated, or extended past the established stability date.
- G. The identification of the actual drug manufacturer/supplier must be identified within the protocol or support documentation, including the full address. The DEA issues yearly manufacturing quotas for all CI controlled substances produced in the US. The protocol bulk demand cannot exceed a reasonable expectation of the manufacturer's total yearly quota. The list of registered manufacturers and their production quota information are published yearly by the DEA in the *Federal Register*. The status of the manufacturing license of the supplier is also verified prior to DEA approval [31].
 - H. For all CI drug substances imported into the US for research purposes the DEA is required to verify manufacturing licensure and "export permit" licensure of the supplier listed in the protocol with that country's drug control agency (e.g., UK: Home Office) and verification that they have the UN reportable manufacturing quota established by the government of that country of origin.
 - I. Drug Supply: It is critical for sound, valid, and reliable research conducted on or with CI substances to utilize bulk material that is manufactured, synthesized, or processed under the FDA's Current Good Manufacturing Practice (CGMP) Guidelines [32]. Legitimate CI drug suppliers hold active CI drug dispensing, distributor or manufacturing licenses. It is the researcher's responsibility to ensure that only CGMP product is used and purchased from a legitimate supplier. Research and manufacturing is designed and codified by law to be independent activities requiring separate registrations (21 CFR §1301.13 (E) [1]). Under this provision, there are "coincident activities" of a researcher that do not require a separate registration.
 - t. A practitioner researcher may manufacture or import drug substances for which a license was issued *if, and only if*, these activities were specifically and detailed in a listed section of the GLP compliant original protocol submitted for registration (21 CFR §1301.18). Additionally, approved and licensed CI researchers may ship and distribute CI drug substances to other CI licensed registrants to conduct research or chemical analysis in that laboratory *if, and only if*, these activities were also specifically detailed in the original protocol submitted to the DEA for the original practitioner's license approval. Most important, and critical to the CI registered practitioner conducting IND- or NDA-enabling research, is that the bulk drug product manufactured and received from another research laboratory *cannot be used* for dose administrations on any nonclinical research study conducted with living animals. CI substances manufactured in a research laboratory, university chemistry laboratory, or private research facility

under a research license *cannot be dosed* in humans or animals. The researcher license allows for a minimum manufacture of drug substance to conduct benchtop stability, pilot scale-up methodologies, analytical method development, or reformulation studies.

NOTE: The implied intent of drug regulatory control policies is to ensure public health and safety, even in nonclinical trials. Once a researcher manufactures enough drug substance for “product development”, further manufacturing activities must be conducted under a separate manufacturing registration where the manufacture registrant must comply with the international requirements as a manufacturer, such as yearly production quota requests for their laboratory/facility as well as end-of-year manufacturing reporting to comply with UN reporting requirements of worldwide production (21 USC §823). Some licensed research laboratories may hold manufacturing licenses, as well. This information is generally included in GLP compliant protocols or in the Quality Assurance Facility Audits required under the GLP regulations conducted as part of the Sponsor’s due diligence approvals of the research laboratory selected for the conduct of the studies. Protocols written in compliance with GLP or GCP regulations sets the stage for an easy review process.

Protocol Development for FDA Review

The FDA staff is required to review and approve the “scientific merits” of all protocols using CI drugs. This review is free of charge to the registrant Table 1 [33,34]. Under the current Manual of Policies and Procedures at CDER (MAPP 6030.9) titled, “Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review” the general review “turn around” time under current policies is approximately 60 to 90 days: It is the FDA alone that has been charged as the only legally-competent regulatory authority to determine if the study design has “merit” and is “scientifically sound”. The CSS serves as FDA’s experts in the area of abuse and dependence [34]. The basis of study design approval is determined:

...on the totality of the publicly available evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement among experts qualified by their scientific training and experience to evaluate such claims, and the claims are supported by such evidence [35].

These criteria for an “adequate and well-controlled study” for purposes of determining the safety and efficacy of a drug is defined under the Code of Federal Regulations (CFR) in 21 CFR §314.126:

- 1) the main objective must be to assess a therapeutically relevant outcome;
- 2) the study must be placebo controlled;
- 3) the subjects must qualify as having the medical condition being studied;
- 4) The study design permits a valid comparison with an appropriate control condition;
- 5) The assignment of subjects to treatment and control groups must be randomized;
- 6) There is minimization of bias through the use of a double-blind study design;
- 7) The study report contains a full protocol and primary data, and
- 8) The analysis of the study data is appropriately conducted.

The protocol must concisely detail the specific objectives of the research proposal (e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology). CSS at FDA must review and approve the goals of the proposed research and estimate the likelihood that the summarized outcome expectations are achievable using the study design described in the protocol, and the results of the proposed research may provide treatment-related significant differences in the general knowledge of safety, efficacy or toxicity of the CI substance. For purposes of NIH policy, a “significant difference” is one of clinical or public health importance, based on substantial scientific data contributed by the study outcome. This definition differs from the commonly used “statistically significant difference,” which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically-significant but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant. The CI protocol is evaluated for “scientific merit” [13]. It is widely accepted that “scientific merit” and research ethics are closely related. In reviewing each protocol for scientific merit, the CSS staff in CDER must ensure the following items are fully addressed by the Sponsor in each protocol:

- 1) The strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed study. Is the prior research that serves as the key support for the proposed project rigorous?
- 2) The protocol should address weaknesses in the rigor of the prior research that serves as the key support for the proposed project. If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
- 3) How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
- 4) The CSS staff will also evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (a) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (b) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (c) interventions to minimize discomfort, distress, pain and injury; and (d) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals [36].

All animal research protocols submitted should have clear objectives and a clearly defined duration. FDA is required to ensure minimal risk to animal or human subjects in any study conducted with CI substances. The term, “minimal risk” means that the probability and magnitude of harm or discomfort anticipated in the study are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations. Similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, IND requirements administered by the FDA or NIH/PHS grants). Members of the CSS in CDER must judge the overall impact to reflect their assessment of the likelihood

for the project to exert a sustained, powerful influence on the research field(s) in accordance with 21 CFR §1301.32. Among pertinent factors that the practitioner should include in their protocols are the following:

- 1) What is the significance of the objectives, specific aims and outcomes of the study. What hypothesis is being tested?
- 2) What is the professional and scientific standing of the SD or Principle Investigator(s) in the community of scientists conducting similar research?
- 3) Is the research innovative? Does the protocol provide a valid avenue to advance the science of the CI substance?
- 4) Is the methodological approach valid and reliable? Are the methods unbiased? Do the methods provide a sound foundation to address the objectives of the study protocol?
- 5) Is the Testing Facility compliant with current GLP requirements or capable of conducting bona fide animal research?

The CSS staff consults with other FDA Review Divisions (such as the Botanical Review Team and others (as listed in FDA’s MAPP 4200.3 Rev. 1): all CDER Offices and Divisions are required to consult CSS to evaluate drugs from an abuse perspective during the review of investigational new drug applications (INDs), new drug applications (NDAs), biological licensing agreements (BLAs), and abbreviated new drug applications (ANDAs) [37]. CDER Offices and Divisions are also required to consult CSS to participate on a multidisciplinary team to evaluate new abuse and dependence related information on currently-marketed drugs. In addition to pre-IND nonclinical research protocol reviews, the CSS performs abuse liability reviews for all INDs and for NDAs of central nervous system-active (CNS-active) drugs with known or potential risk for abuse and dependence. It is the task of the CSS staff to perform the reviews concerning all nonclinical protocols submitted for CI controlled substances including drug abuse liability (DAL) studies required for schedule control actions initiated during NDA review. As is standard in all GLP-compliant protocols a set of complete and detailed justification sections should be included with all requisite reference citations for the following:

- 1) Justification for Test Article / Positive Control Article Selection: The current thinking of the FDA on CI substance use on a study requires full identification of all test and control articles and their vehicles in the protocol. The full characterization of the test and control article formulations is required. This includes quantitative concentration, homogeneity (top, middle, bottom strata concentration comparisons), and stability verifications. Vehicle and components of vehicles that are purchased from legitimate medical supply sources may be limited to the information supplied on the label of these commercially available products, but test article characterization must be detailed and quantitative.

- 2) Justification for the Use of Schedule I Drug: If a lower scheduled drug can be used for positive comparators (CII to CV), they should be used. A detailed justification for the use and selection of a CI drug must be included in the protocols. This section should be included under the Test Article characterization header and the Positive Control Article characterization headers if both are CI drugs. Justification must be a detailed defense for the drug selection AND a detailed defense as to why other CII – CV drugs *are not chosen* to be used. Included in the justification for the use of a Schedule I drug should be a defense for not using a non-controlled comparator. For example, LSD may be proposed as a positive comparator in a study selected for LSD’s putative 5HT2 agonist binding characteristics. In comparison, the phenethylamine, 2,5-dimethoxy-4-iodoamphetamine (DOI), a noncontrolled drug, has a better binding profile for the 5HT2 site and may be a better comparator in this study. Additionally, the justification for using a Schedule I drug comparator should include a defense of not using a lower scheduled comparator. For example, if heroin (CI) is proposed for the positive comparator in the study, justification would be needed to explain why another less restricted CII opiate like morphine, methadone, or oxycodone was not chosen. The practitioner must play “devil’s advocate” and build a full evidence-based, scientifically sound justification for each of the specific CI drugs selected for inclusion in the protocols.
- 3) Justification for the Selection of Animals: When nonclinical study designs require only one species the harmonized regulatory preference is the rodent. The second species selected for the studies required to have rodent and non-rodent species should be justified with the caveat that a smaller bodyweight requires less bulk material (dog vs NHP, etc.). The total number of animals used on the study should be based on standard regulatory guideline requirements or based on the results of a formal statistical “power analysis”. The current thinking of the agency is the inclusion of both male and female animal subjects; if only one sex is included in the study design then justification for the selected sex must be included in the protocol. Formal justification for the age and bodyweights of the animal subjects must also be addressed in the protocols.
- 4) Justification for the Route of Administration: The route-of-administration may be selected based on systemic exposure targets, the intended route-of-administration in human patients, or the standard route-of-administration for the nonclinical assay being proposed. The scientific basis for selection must also consider CI bulk weight needed to complete the study. The study must use the targeted route that will require the lowest bulk demand of the CI substance that will be required to conduct the study. For example, food admixtures provide uncontrollable factors that increase the likelihood

Description	Recommended Timeline	Type of Evaluation	Response to Sponsor
Nonclinical			
Nonclinical Priority amendments, supporting new clinical protocols (general, genetic, reproductive toxicology reports) Standard (toxicology studies by routes of administration other than planned clinical route, pharmacology, abuse / dependence)	Reviewer/team leader should screen within 7 business days of receipt to determine priority status and level of review: • Priority amendments: preliminary evaluation within 14-30 days; review up to 180 days. • Standard: within 6 to 12 months	•Written review for priority •Written review as needed for nonpriority	As Needed.

Table 1: MAPP 6030.9 IND Drug Development Submissions [38].

of drug loss, diversion, and environment contamination in nonclinical study designs. The detailed justification of these factors is needed for drug control and scientific merit assessments.

Conclusion

The current manual of policies and procedures at CDER (MAPP 7400.1 rev 2) titled, "Management of the CDER Pharmacology/ Toxicology Coordinating Committee and Its Associated Subcommittees and Working Groups" establishes administrative policies that is relevant to the role CDER plays in the existing Interagency Committee on Drug Control (ICDC) which is comprised of members from CDER staff, the Office of National Drug Control Policy (ONDCP), National Institutes on Drug Abuse (NIDA) and members of the Drug Enforcement Administration. The committee regularly meets to discuss, in part, the submission, review, and approvals of Schedule I research protocols from universities, the biotechnology and pharmaceutical industry, as well as private/public research institutions. Research conducted with drug substances under International and federal schedule control status listed in the CSA may not necessarily require any additional costs, labor, or effort when compared to standard GLP-compliant research conducted with CII, CIII, or CIV drug substances. All protocols for conducting research with CI substances must simply be submitted to the DEA and FDA for review prior to purchasing bulk test or control articles for the study. These protocols include discovery, efficacy (both non-GLP), pre-IND (i.e., dose range finding), IND-, and NDA- enabling studies conducted with animals (GLP compliance asserted). Under the current policies and procedures in the US, nonclinical research programs in established research laboratories conducted under GLP-compliance are easily amenable to regulatory review for CI drug substances simply using the standard protocol language, formatting, and review processes already in use during protocol development with a pharmaceutical sponsor. The published reports claiming that current US drug control policies hinder, restrict, or obstruct bona fide research with CI substances has not been our experience. Our history in the nonclinical research arena with CI drug substances has proven the guaranteed access to CI drugs established by the CSA and 1961 Drug Treaty for legitimate medical use and biomedical research remains intact. The current resources provided by both the FDA and DEA to practitioners interested in conducting research with schedule-controlled drugs are often overlooked and represent a most valuable and untapped source of information that can ease the path to IND and NDA approvals.

Conflicts of Interest

There are no conflicts of interest for any author of this manuscript. The preparation of the manuscript and the conduct of the study plans are considered a coincident function of employment. No grant or outside financial funding was associated with the development or reporting of these data.

References

1. United Nations (1961) Single Convention on Narcotic Drugs.
2. Drug Enforcement Administration (1992) Marijuana Scheduling Petition; Denial of Petition; Remand. *Federal Register* 57: 10499-10508.
3. Cohen PJ (2009) Medical Marijuana: The Conflict between Scientific Evidence and Political Ideology Part One of Two. *J Pain & Palliat Care Pharmacother* 23: 4-25.
4. Cohen PJ (2009) Medical Marijuana: The Conflict Between Scientific Evidence and Political Ideology Part Two of Two. *J Pain & Palliat Care Pharmacother* 23: 120-140.
5. Leshner AI (1995) Personal Communication to Dr. I Abrams. Transcribed NIDA rejection letter, dated April 19, 1995 from Dr. Alan Leshner (NIDA Director) to Dr. Donald Abrams.
6. Drug Enforcement Administration (2016) Rosenberg C (Administrator of the DEA) Personal Communication to the Honorable Gina M. Raimondo, Governor of Rhode Island, the Honorable Jay R. Inslee, Governor of Washington and Mr. Bryan A. Krumm. Rejection of petition to reschedule marijuana.
7. Food and Drug Administration (2017) Investigational New Drug (IND) Application. Retrieved from March 2019.
8. Center for Drug Evaluation and Research (2010) CDER 21st Century Review Process Desk Reference Guide.
9. Food and Drug Administration (2005) Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products.
10. Food and Drug Administration (2012) PDUFA Reauthorization Performance Goals and Procedures for Fiscal Years 2013 Through 2017.
11. Food and Drug Administration (2016) Pre-IND Consultation Program.
12. Drug Enforcement Agency (2018) Controlled Substances by DEA Drug Code.
13. Rizzo-Parse R (2016) Scientific Merit: Integrity in Research. *Nursing Sci Quarterly* 29: 5.
14. Drug Enforcement Administration. National Media Affairs Office (2018) DEA Speeds Up Application Process For Research On Schedule I Drugs.
15. Nutt D (2015) Illegal Drugs Laws: Clearing a 50-Year-Old Obstacle to Research. *PLoS Biology* 13: e1002047.
16. Nutt DJ, King LA, Nichols DE (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Rev: Neurosci* 14: 577-85.
17. Nutt DJ, King LA, Nichols DE (2013) New victims of current drug laws. *Nature Rev: Neurosci* 14: 877.
18. Nutt DJ (2010) Necessity or nastiness? The hidden law denying cannabis for medical use.
19. Graves DE (2018) Cannabis shenanigans: advocating for the restoration of an effective treatment of pain following spinal cord injury. *Spinal Cord Ser Cases* 4: 67.
20. Freeman TP, Mehta MA, Neill JC, Nutt DJ, Tunbridge EM, et al. (2018) Restrictions on drugs with medical value: Moving beyond stalemate. *J Psychopharmacol* 32: 1053-1055.
21. Green AR, Nutt DJ (2014) Pharmacology should be at the centre of all preclinical and clinical studies on new psychoactive substances (recreational drugs). *J Psychopharmacol* 28: 711-718.
22. Warner KE (1991) Legalizing drugs: lessons from (and about) economics. *Milbank Q* 69: 641- 661.
23. Sessa B, Nutt DJ (2007) MDMA, politics and medical research: have we thrown the baby out with the bathwater. *J Psychopharmacol* 21: 787-791.
24. Wiley J L, Marusich JA, Huffman JW, Balster RL, Thomas BF, et al. (2011) Hijacking of basic research: The case of synthetic cannabinoids. *Methods Report* (RTI Press).
25. Nichols D (2011) Legal highs: the dark side of medicinal chemistry. *Nature* 469: 7.
26. Daily Mail (2011) Chemist horrified to find his pioneering work with psychedelic drugs turned into deadly 'legal highs'.
27. Stewart AM, Kalueff AV (2013) Controlled substances and innovation of biomedicine: a preclinical perspective. *Nature Rev: Neurosci* 14: 877.
28. Drug Enforcement Agency (2018) Controlled Substances Security Manual.
29. Cowley S (2015) How Wayne State Police Helped Breathe Life Into a Blighted Detroit Strip. *NY Times*, February 25, 2015.
30. de Leon E, Schilling J (2017) Urban Institute Research Report: Urban Blight and Public Health Addressing the Impact of Substandard Housing, Abandoned Buildings and Vacant Lot.
31. Drug Enforcement Administration (2018) Control Substance Quotas. Final Rule. *Federal Register* 83: 32784-32790.
32. Food and Drug Administration (2018) Current Good Manufacturing Practice (CGMP) Regulations.

33. Controlled Substance Staff (2003) Consulting the Controlled Substance Staff on INDs and Protocols That Use Schedule I Controlled Substances and Drugs.
34. Controlled Substance Staff (2018) Controlled Substance Staff Functional Roles.
35. Food and Drug Administration (2009) Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims.
36. National Institutes of Health (2019) NIH & AHRQ Announce Upcoming Updates to Application Instructions and Review Criteria for Research Grant Applications.
37. Throckmorton DC (2016) Testimony before the Subcommittee on Crime and Terrorism Committee on the Judiciary, US Senate; July 13, 2016.
38. <https://www.fda.gov/media/85790/download>